Remarks

Claims 5, 9, and 43, are pending and under examination in the subject application, with claims 17-42 withdrawn from consideration. By this Amendment, applicants have hereinabove canceled claims 17-42 without prejudice or disclaimer to applicants' right to pursue the subject matter of these claims in a future continuation or other application, and have amended claims 5, 9 and 43. Support for the amendments to claim 5 can be found in the specification at, *inter alia*, page 3, lines 2-5; page 15, lines 1-3; page 5, lines 20-25; page 5, line 3 and line 28; and page 1, lines 21-22. Support for the amendments to claim 9 can be found in the specification at, *inter alia*, page 3, lines 2-5; page 15, lines 1-3; page 5, lines 20-25; page 5, line 3 and line 28; and page 1, lines 21-22. Support for the amendments to claim 43 can be found in the specification at, *inter alia*, page 19, line 15-18. Applicants maintain that the Amendments to the claims raise no issue of new matter, and respectfully request entry of this Amendment. Accordingly, after entry of this Amendment, claims 5, 9 and 43 will be pending and under examination.

Claims Rejected Under 35 U.S.C. §112 (First Paragraph)

The Examiner stated that Claim 43 remains rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for using the pharmaceutical compositions of the instant invention in an in vitro method, does not reasonably provide enablement for using the claimed pharmaceutical compositions *in vivo* for therapeutic purposes. The Examiner stated that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly

connected, to use the invention commensurate in scope with this claim, for the reasons of record set forth in the Office Action mailed 6-18-03. The Examiner stated that applicants' arguments filed 9-22-03 have been fully considered but they are not persuasive. The Examiner stated that applicants traverse the instant rejection on the grounds that "the claimed active antisense, though they may vary in the extent they down regulate protein expression, all are active in the different cell lines regardless of delivery agent. Applicants also note that the therapeutic activity of the claimed oligonucleotides is defined by their sequence - control sequences do not work (see specification, page 22, lines 5-6)." The Examiner stated that, furthermore, applicants argue that different levels of inhibition does not preclude activity or usefulness. The Examiner stated that, contrary to applicants' assertions, it is first noted that the instant claims do not recite any particular mRNA target for the claimed antisense oligonucleotides, nor do they recite any particular length for the claimed antisense oligonucleotides. The Examiner stated that the instant claims merely recite antisense oligonucleotides comprising nucleotide sequence A, B, C, D, E, F, G, H, I, J, K, L or M (SEQ ID NO: 1-13), respectively, wherein the oligonucleotide is conjugated to a peptide or comprises an -Ome group at their 2' position. The Examiner stated that, however, applicants have not demonstrated how to use an antisense oligonucleotide of an unknown length (for example 100 nucleotides in length), wherein said oligonucleotide is conjugated to a peptide of unknown composition, or comprising 2'-Ome modifications, for therapeutic purposes. The Examiner stated that although applicants have demonstrated some *in vitro* inhibition of bcl-xL there is no evidence that these effects are correlated with any phenotypic changes in the cells that are treated with the antisense oligonucleotides 18-20 nucleotides in length. The Examiner stated that furthermore, due to the unpredictability

associated with the behavior of antisense oligonucleotides in a cellular environment, as it relates to the sequence composition, sequence length, and modifications as described in the previous Office Action, applicant's *in vitro* observations can not be used to predict the pharmacokinetic behavior of the antisense oligonucleotide *in vivo*, or provide evidence of therapeutic utility. The Examiner stated that as stated in the prior Office Action, it is concluded that the amount of experimentation required for the skilled artisan to practice the full scope of the claimed invention would be undue based upon the known unpredictability regarding the delivery of antisense *in vivo* and further with the production of secondary effects such as treating a disease associated with the expression of a gene, and the lack of guidance in the specification as filed in this regard. The Examiner stated that the deficiencies in the specification would constitute undue experimentation since these steps must be achieved without instructions from the specification before one is enabled to practice the claimed invention.

In response, applicants respectfully traverse the Examiner's rejection. However, in order to expedite prosecution, but without conceding the correctness of the Examiner's position, applicants have hereinabove amended claims 5 and 9, on which claim 43 is dependent, to recite "consisting essentially of" language and "consisting" language, respectively, and to recite a functional characteristic of the claimed oligonucleotide. Applicants note that working examples are provided in the specification, and that the claim language distinguishes over oligonucleotides of unknown length that do not inhibit translation of bcl-xL-encoding mRNA. In addition, applicants note that the cited Branch reference does not teach that an antisense active *in vitro* has no activity *in vivo*, merely that it may be a different activity. In fact, Crooke et al., previously cited by the Examiner, shows numerous examples

of antisense with *in vivo* activity (see Table 1). In addition, applicants note that Crooke et al. discuss antisense *in vitro* that have been successful *in vivo* (see page 22, Crooke et al.) Applicants further note that dosage determination is a standard clinical skill required of every pharmaceutical and routine to one of skill in the art, and although possibly requiring some experimentation, does not require undue experimentation. Furthermore, the actual pharmacokinetics do not need to be predicted, as the Examiner has suggested, merely the appropriate dosage measured empirically using routine skills. Moreover, only a "reasonable correlation between the disclosed *in vitro* utility and an *in vivo* activity" is required for enablement (M.P.E.P. §2164.03) which applicant has shown, and the known role of bcl-xL in intimal lesion formation, and the clear demonstration of bcl-xL expression inhibition by applicants, clearly shows a reasonable correlation that Examiner has not countered with indications of non-correlation. Accordingly, applicants maintain that the claims are not properly rejected under 35 U.S.C. §112, and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Claims Rejected Under 35 U.S.C. §112 (First Paragraph)

The Examiner stated that claim 43 is rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The Examiner stated that the claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The Examiner stated that claim 43 is drawn to a pharmaceutical composition comprising an effective amount of an antisense oligonucleotide analog thereof of claim 5 or 9 and a

pharmaceutically acceptable carrier, wherein the effective amount is between 0.1 μM and 10 μM. The Examiner stated that it is noted that the scope of this claim encompasses antisense oligonucleotides or analogs of unknown length and composition. The Examiner stated that according to the specification as filed the antisense oligonucleotides of the present invention are disclosed as being functional to reduce or eliminate the expression of bcl-xL (see page 1, lines 19-20). The Examiner stated that however, the instant claims do not recite this particular functional limitation. The Examiner stated that the instant claims read on antisense oligonucleotide, i.e. one targeting any particular gene, from any particular organism, including all polymorphic and allelic variants of the claimed sequences. The Examiner stated that one of ordinary skill in the art would not be able to predict the structures of all nucleotide sequences encompassed by the instant claims, because they comprise a broad number of nucleotide sequences, and there is no common structure shared among the species that is related to any particular common function, i.e. to reduce or eliminate the expression of bcl-xL, and such that the ordinary skilled artisan would be able to immediately envision all analogs of the sequences encompassed by the instant claims, such that said analogs are functional antisense oligonucleotides without the need for further experimentation. The Examiner further stated that applicants have not provided the nucleotide structures of the full scope of analogs of the antisense oligonucleotides encompassed by the instant claims, and that it is evident that further experimentation would be required in order to identify the full scope of oligonucleotides encompassed by the claimed invention. The Examiner stated that, therefore, it is concluded that applicants were not in possession of the full scope of the claimed antisense oligonucleotides at the time of filing of the instant application.

In response, applicants respectfully traverse the Examiner's rejection. However, in order to expedite prosecution, but without conceding the correctness of the Examiner's position, applicants have hereinabove amended claim 5, on which claim 43 is dependent, to recite both "consisting essentially of" language and to recite a functional characteristic of the claimed oligonucleotide, and have amended claim 9, on which claim 43 is dependent, to recite both "consisting of" language and to recite a functional characteristic of the claimed oligonucleotide. Applicants maintain that the functional language recited in the claims, namely inhibition of bcl-xL-encoding mRNA translation, as well as the structural information, recited by way of SEQ ID NOs., more clearly defines the claimed subject matter. Accordingly, applicants maintain that the claims are not properly rejected under 35 U.S.C. §112, and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Double Patenting

The Examiner stated that claims 5, 9 and 43 remain provisionally rejected under the judicially created doctrine of double patenting over claims 9, 36-50, 53-54, 58, and 61-62 of copending Application No. 09/832,648 in view of Manoharan et al., Sanghvi et al., Matteucci et al. and Arnold et al. for the reasons of record set forth in the prior Office Action mailed 6-18-03, that applicants' arguments filed 9-22-03 have been fully considered but they are not persuasive. The Examiner stated that applicants traverse the instant rejection on the grounds that the double patenting rejection made by the Examiner in the June 18, 2003 Office Action becomes moot because the Examiner's arguments are premised on sequences not cited in the pending claims. The Examiner stated that accordingly, applicants request that the

Examiner reconsider and withdraw this ground of rejection. The Examiner stated that applicants' response is confusing since SEQ ID NO:4 is still recited in the current claims as amended, and in the claims of copending application 09/832,648.

In response, applicants respectfully traverse the Examiner's rejection. Specifically, applicant notes that the claims of the copending application 09/832,648 recite elements, namely 2'-OMe modifications, that are unobvious over the claims as hereinabove amended. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Claims Rejected Under 35 U.S.C. §103(a)

The Examiner stated that claims 5, 9 and 43 are rejected under 35 U.S.C. §103(a) as being unpatentable over Pollman et al. in view of Gibbons et al. (US Patent No. 5,776,905). The Examiner stated that claims 5 and 9 are drawn to antisense oligonucleotides comprising nucleotide sequence A, B, C, D, E, F, G, H, I, J, K, L or M (SEQ ID NO: 1-13), respectively, wherein the oligonucleotide is conjugated to a peptide or comprises an -OMe group at their 2' position. The Examiner stated that claim 43 is drawn to a composition comprising an effective amount of an antisense oligonucleotide or analog thereof, and a pharmaceutically acceptable carrier, wherein the effective amount is between 0.1 μM and 10 μM. The Examiner further stated that Pollman et al. teach inhibition of neo-intimal cell bcl-xL expression comprising transfecting a solution comprising Lipofectamine and an antisense oligonucleotide directed against bcl-xL into atheromatous (i.e. vascular) lesions in the rabbit carotid artery (Methods section, p. 226). The Examiner stated that specific downregulation of the bcl-xL splice isoform resulted in regression of atheromatous lesions (see Figure 8, page 226). The Examiner also stated that

additionally, Pollman et al. discloses 3 phosphorothioate modified antisense oligonucleotides, wherein antisense sequence-3 (#3; see Methods section, page 226) comprises the consecutive nucleotide sequence of SEQ ID NO: 2 of the instant application. The Examiner stated that however, Pollman et al. does not teach antisense oligonucleotides conjugated to a peptide or wherein one or more of the oligonucleotide's sugars contain an -Ome group at their 2'-position. The Examiner stated that additionally, Pollman et al. does not teach pharmaceutical compositions comprising an effective amount of an antisense oligonucleotide, wherein the effective amount is between 0.1 μM and 10 μM. The Examiner stated that additionally, Gibbons et al. teach a method for reducing the dimensions of a neointimal vascular lesion in a patient comprising localized delivery of an antisense oligonucleotide that inhibits the expression of bcl-xL (col.2 lines 28-42). Gibbons et al. teach administration of antisense oligonucleotides comprising methods known in the art for enhancing the uptake if nucleic acids by cells, for example delivery systems include Sendai virus-liposomes, cationic liposomes polymeric gels or matrices, and porous balloon catheters (col. 7, lines 45-60). Gibbons et al. teach that the antisense oligonucleotides used in the method for reducing the expression of bcl-xL in cells may comprise modifications to enhance oligonucleotide intracellular stability and binding affinity. The Examiner further stated that in a specific embodiment Gibbons et al. teach that the 2'-OH ribose sugar may be altered to form 2'-O-methyl (col. 5, lines 6-28). [It is noted, stated the Examiner, that since the specification as filed does not clearly define what the term "-OMe" is intended to encompass, this term is interpreted as encompassing either "2'-O-methyl" or "2'-O-methoxy."] The Examiner stated that the oligonucleotides of Gibbons et al. can also be conjugated to poly-L-lysine (considered a peptide) or other polyamines to enhance delivery to cells (see col. 5, lines

52-56). The Examiner stated that, moreover, Gibbons et al. teach that compounds having the desired pharmacological activity may be administered in a physiologically acceptable carrier to a host for treatment intimal lesions. The Examiner stated that depending upon the manner of introduction, the compounds may be formulated in a variety of ways. The concentration of therapeutically active compound in the formulation may vary from about 0.1-100 wt. % (col. 7, lines 19-25). The Examiner additionally stated that it would have been obvious to one having ordinary skill in the art at the time the invention was made, to design the antisense oligonucleotide according to the present invention comprising a sequence according to A, B, C, D, E, F, G, H, I, J, K, L or M (SEQ ID NO: 1-13), respectively, wherein the oligonucleotide is conjugated to a peptide or comprises an -OMe group at their 2' position. The Examiner stated further that one of ordinary skill in the art would have been motivated to specifically design antisense oligonucleotides comprising the sequence according to SEQ ID NO:2 (B), since this sequence is expressly disclosed by Pollman et al. as being effective to inhibit the expression of bcl-xL mRNA. The Examiner also stated that, additionally, one of ordinary skill in the art would have been motivated to modify the sequence disclosed by Pollman et al. to be conjugated to a peptide or further to comprise a 2'-OMe sugar modification, since Gibbons et al. teach these modifications would enhance the cellular properties of antisense oligonucleotides targeting bcl-xL. The Examiner stated that moreover, in regards to the claimed effective amount of antisense oligonucleotide recited in the composition of claim 43, specifically wherein the effective amount is between 0.1 μM and 10 μM, absent evidence to the contrary, the teachings of Gibbons et al. which states that the concentration of active compounds used in the design of formulations comprising antisense oligonucleotides, may vary from about 0.1-100 wt.% (col. 7, lines 19-25), encompasses applicants

claimed range of between 0.1 μM and 10 μM. The Examiner stated that therefore, the invention as a whole would have been *prima facie* obvious at the time the invention was made over Pollman et al. in view of Gibbons et al.

In response, applicants respectfully traverse the Examiner's rejection. Specifically, with regard to claim 5, applicants note that Pollman et al. does not teach all the elements of applicants' claimed invention, namely the sequences referred to in claim 5, and Gibbons et al. does not remedy this deficiency. In addition, Pollman et al. has a longer sequence than SEQ ID NO:2 recited in amended claim 9, and Gibbons et al. does not remedy this deficiency. Moreover, it is hard to predict the efficacy of a given antisense molecule as demonstrated by applicants' results shown in Figure 6. Accordingly, applicants maintain that the claims are not obvious over Pollman et al. in combination with Gibbons et al., and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorneys invite the Examiner to telephone them at the number provided below.

No fee is deemed necessary in connection with the filing of this Amendment. If any fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

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